# The Bethesda System

## A Proposal for Reporting Abnormal Cervical Smears Based on the Reproducibility of Cytopathologic Diagnoses

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**• In the Bethesda System, noninvasive squamous abnormalities are classified as atypical squamous cells of undetermined significance (ASQUS), low-grade squamous intraepithelial lesions, and high-grade squamous intraepithelial lesions. The Bethesda System eliminates two diagnostic distinctions that are made in the dysplasia/carcinoma in situ and cervical intraepithelial neoplasia (CIN) classifications, CIN1 vs koilocytotic atypia and CIN2 vs CIN3, and maintains three others, negative vs ASQUS, ASQUS vs koilocytotic atypia, and CIN1 vs CIN2. To determine whether the diagnostic distinctions preserved in the Bethesda System are made more consistently than those eliminated, we analyzed the interobserver reproducibility of two cytopathologists in classifying 257 smears. The findings indicate that the distinctions retained in the Bethesda System are more reproducible than those eliminated. Specifically, cases classified as koilocytotic atypia were distinguished from CIN1 no more reproducibly than predicted by chance, whereas CIN2 and CIN3 were distinguished as consistently as any other pair of diagnoses examined. In 13 cases in which there was interobserver discordance, one reviewer classified the smear as ASQUS and the other reviewer diagnosed CIN2 or CIN3. The findings in this study suggest that smears showing koilocytotic atypia and/or CIN1 may be reported as low-grade squamous intraepithelial lesions without further specification. In contrast, smears showing high-grade squamous intraepithelial lesions may be further classified as CIN2 or CIN3 in accordance with the Bethesda guidelines. Since the diagnosis of ASQUS is applied to smears showing a wide spectrum of changes, management of patients with the diagnosis of ASQUS will be facilitated by providing an explanatory note and/or recommendations when appropriate.**

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The Bethesda System was developed to provide a simple, unambiguous classification for reporting cervical smears. In the Bethesda System, noninvasive squamous lesions are classified as atypical squamous cells of undetermined significance (ASQUS), low-grade squamous intraepithelial lesions (LSILs), and high-grade squamous intraepithelial lesions (HSILs).[1] Atypical squamous cells of undetermined significance is used to designate squamous cells with abnormal nuclear features that fall short of koilocytotic atypia (KA) and cervical intraepithelial neoplasia (CIN1), but exceed those usually associated with inflammation and repair. The designation *low-grade squamous intraepithelial lesion* encompasses lesions previously classified as KA and CIN1; HSIL subsumes CIN2 and CIN3.

The Bethesda System contains fewer diagnostic categories than dysplasia/carcinoma in situ (CIS) and CIN classifications, hence implementation of the Bethesda System will inevitably promote higher interobserver agreement simply due to having fewer classification categories. Ideally, the Bethesda System should also improve interobserver reproducibility by maintaining diagnostic distinctions that observers recognize consistently and eliminating those that are frequent sources of disagreement. In this study, the diagnostic agreement of two cytopathologists was analyzed to determine which aspects of the Bethesda System promote consistent interpretation of cytologic specimens. These results may be useful in devising an optimal method of reporting cervical smears using the Bethesda guidelines.

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## MATERIALS AND METHODS

### Case Selection and Review

Two hundred fifty-seven cervical specimens accessioned at The Johns Hopkins Hospital, Baltimore, Md, laboratory of cytopathology between July 1, 1989, and June 30, 1990, were selected by reviewing an alphabetized file of reports arranged by patients' last names. Case selection was based on the originally assigned diagnoses using the CIN classification. The study set included 80 cases classified as ASQUS, 80 cases of CIN1 and/or KA, 40 specimens diagnosed as CIN2, and 30 classified as CIN3. Twenty-

**Table 1.—Cytopathologic Diagnoses***

| Reviewer B | Reviewer A: Negative | ASQUS | KA | CIN1 | CIN2 | CIN3 |
|---|---|---|---|---|---|---|
| Negative | 7 | 14 | 1 | 2 | 0 | 0 |
| ASQUS | 9 | **53** | 2 | 20 | 6 | 1 |
| KA | 0 | 12 | **7** | 28 | 1 | 0 |
| CIN1 | 0 | 14 | 2 | **18** | 4 | 4 |
| CIN2 | 0 | 2 | 2 | 7 | **8** | 2 |
| CIN3 | 0 | 4 | 1 | 3 | 6 | **17** |

*ASQUS indicates atypical squamous cells of undetermined significance; KA, koilocytotic atypia; and CIN, cervical intraepithelial neoplasia.

seven cases diagnosed as either CIN 1 to 2 or CIN 2 to 3 were encountered during the search and were also included. Cases originally classified as negative or reactive were excluded. Eighty-seven specimens were obtained with an Ayre spatula in combination with a cytobrush and 170 were procured with a spatula alone. The specimens were prepared as one or two smears and fixed in 70% ethanol. Colposcopically directed smears and specimens obtained from women older than 60 years were excluded. The cytotechnologists' original marks indicating the presence of abnormal cells were left in place. The cases were randomly numbered to conceal the original labels and then examined independently by two of us (M.E.S. and Y.S.E.), who classified the cases as negative, ASQUS, KA, CIN1, CIN2, or CIN3.

### Data Analysis

The Bethesda System eliminates two distinctions that are part of the CIN classification as conventionally employed in cytopathology, KA vs CIN1 and CIN2 vs CIN3, and maintains three others, negative vs ASQUS, ASQUS vs KA, and CIN1 vs CIN2. To examine the reproducibility with which two cytopathologists can make these separations, we created data sets consisting of cases in which both reviewers had rendered one of the two diagnoses listed in the pairs above. Thus, the interobserver reproducibility obtained within each data set reflected the consistency with which two adjacent categories in the CIN classification hierarchy could be distinguished. Two category disagreements were excluded from this part of the analysis because the Bethesda System does not eliminate any distinctions between diagnostic categories that are not adjacent in the CIN classification. The interobserver agreement for the cases within each data set was computed. Since each set consisted of two possible diagnoses, random agreement was defined as 50% interobserver concordance and perfect interobserver reproducibility as 100% agreement.

## RESULTS

### Interobserver Agreement

The reviewers rendered the same diagnosis in 110 (42.8%) of 257 cases (Table 1). In 86 (33.5%) cases the reviewers disagreed by one category and in 61 (23.7%) by two or more categories. Thirty-three (12.8%) cases were classified as negative by one or both reviewers. Among these 33 cases, a two-category discrepancy was found in only three (9.1%). Two-category disagreements were common among all of the remaining cases. Translating the original diagnoses into the Bethesda classification, there were 148 (57.6%) exact agreements: seven negative, 53 abnormal squamous cells of undetermined significance, 55 LSILs, and 33 HSILs.

### Reproducibility of Diagnostic Categories Maintained vs Those Eliminated

Table 2 displays the level of interobserver agreement for each set of cases in which both reviewers rendered either

**Table 2.—Reproducibility of Diagnostic Categories Retained and Eliminated in the Bethesda System***

| | Agreement, No. (%) |
|---|---|
| **Diagnostic Distinctions Retained in the Bethesda System** | |
| Negative-ASQUS | 60/83 (73) |
| ASQUS-KA | 60/74 (81) |
| CIN1-CIN2 | 26/37 (70) |
| **Diagnostic Distinctions Eliminated in the Bethesda System** | |
| KA-CIN1 | 25/55 (45) |
| CIN2-CIN3 | 25/33 (76) |

*ASQUS indicates atypical squamous cells of undetermined significance; KA, koilocytotic atypia; and CIN, cervical intraepithelial neoplasia.

of two diagnoses occupying adjacent positions in the CIN classification hierarchy. The diagnostic distinction between CIN2 and CIN3 was made as reproducibly as any of the distinctions retained in the Bethesda System. In contrast, the reviewers concurred in the distinction between KA and CIN1 no more frequently than predicted by chance. The distinctions retained in the Bethesda System were therefore more reproducible than those eliminated.

## COMMENT

This study demonstrates that the diagnostic distinctions retained in the Bethesda System are more reproducible than those eliminated. This result primarily reflects the poor rate of interobserver agreement in distinguishing KA from CIN1 in this analysis. The Working Party for the British Society for Clinical Cytology reached a similar conclusion regarding the distinction of KA and CIN1.[2] Since 97% of these lesions contain human papillomavirus DNA when studied by the polymerase chain reaction or Southern blot hybridization, the addition of terms such as koilocytosis or changes consistent with human papillomavirus to denote the presence of cytoplasmic vacuolization is unnecessary (M. H. Schiffman, MD, H. M. Bauer, MPH, R. N. Hoover, MD, et al, unpublished data, 1992). Accordingly, we advocate the use of the term LSIL without further qualification.

The validity of employing the designation LSIL to refer to smears showing KA and/or CIN1 is also supported by virologic, epidemiologic, and clinical evidence. Human papillomavirus has been isolated with nearly identical frequency from patients with either CIN1 or KA,[3] and the spectrum of viral types identified in these patients is similar.[4,5] In addition, the demographic characteristics of patients with KA and CIN1 are indistinguishable (M. H.

Schiffman, MD, H. M. Bauer, MPH, R. N. Hoover, MD, et al, unpublished data, 1992). Finally, studies have demonstrated that a similar proportion of patients with either KA or CIN1 develop high-grade SIL if not treated (N. B. Kiviat, MD, personal communication, 1991).[6-8] In summary, all available evidence indicates that patients with KA or CIN1 should be managed in the same manner and that cytopathologic separation of these lesions is unnecessary. We believe that inclusion of KA in the LSIL category should not lead to unnecessary referrals of patients for colposcopy if the diagnosis of LSIL is reserved for cytopathologic specimens displaying diagnostic nuclear abnormalities.[9] Potential difficulties resulting from misinterpretation of minor cytologic abnormalities such as KA are unrelated to the diagnostic classification employed and can be avoided by using strict criteria for the diagnosis of squamous intraepithelial lesions.

This study indicates that cytopathologists are capable of distinguishing CIN2 from CIN3 as consistently as they can distinguish any other pair of closely related lesions. Hence, we advocate the use of the term HSIL in conjunction with the specific designations of CIN2 and CIN3, as is currently permitted under the Bethesda guidelines.[1] Since the treatment of squamous intraepithelial lesions is based primarily on the size and distribution of cervical lesions,[10] we believe that clinical care is not compromised by using the HSIL terminology. In addition, the HSIL terminology highlights the importance of recognizing CIN2 and CIN3 lesions that are generally composed of small cells that may be easily overlooked in cytologic screening.[11] If the discrepancy between a cytopathologic diagnosis of LSIL and a histopathologic diagnosis of CIN2 (HSIL) is considered as clinically significant as a two-category discrepancy in the CIN or dysplasia/carcinoma in situ classification, cone biopsies may be performed more frequently to rule out colposcopically occult high-grade lesions. In our opinion, unnecessary cone biopsies can be avoided in most cases by demonstrating through cytologic-histologic correlation that the abnormal cells in the cytologic and histologic preparations are from the same lesion despite an apparent discrepancy in the original independently assigned diagnoses.

Numerous studies have demonstrated that interobserver agreement in classifying abnormal smears is less than ideal.[12-17] In this study, use of the Bethesda System compared with the CIN classification increased the level of exact agreement by only 15% (43% to 58%). The distinction of ASQUS from reactive changes and LSIL remains an important cytopathologic and clinical problem in the Bethesda System. In this study, 13 cases diagnosed as ASQUS by reviewer A or B were classified as CIN2 or CIN3 by the other observer. These data underscore the importance of further qualification of a diagnosis of ASQUS to communicate information for appropriate clinical management.

Historically, the use of the term *atypia* has been inconsistent and ambiguous. Frisch[18] theorized that atypical squamous cells may represent a precursor of CIN or a marker of patients at risk for CIN, but concluded that at least some examples result from underreading of cytopathologic specimens. Based on the frequent discovery of CIN and invasive carcinoma shortly after a diagnosis of squamous atypia, Melamed and Flehinger[19] postulated that atypical smears frequently reflect inadequate sampling of advanced lesions. Cervical intraepithelial neoplasia or invasive carcinoma have been reportedly found in 13.5% to 70% of patients with cytopathologic diagnoses of "squamous atypia" as variously defined by different authors.[20-33]

Application of the term *atypia* is highly restricted in the Bethesda System. Although some lesions previously designated as squamous atypia would now qualify as ASQUS, the majority do not. Thus, only lesions displaying unclear abnormalities that do not correspond to those in SIL but are more marked than those attributed to inflammation and repair should be included in this category.

Since patients who have a negative repeat smear following an initial atypical smear may harbor serious lesions,[21-23,25,27,30-33] some gynecologists routinely colposcope all patients with abnormal smears. In contrast, since many cases of ASQUS appear to represent reparative processes, not associated with malignancy, other gynecologists follow a smear showing ASQUS with a repeat smear in 3 to 6 months. There continues to be considerable confusion over the significance of this diagnosis, and consequently, the management of these smears is inconsistent and problematic. Accordingly, we suggest that providing an explanatory note with follow-up recommendations may facilitate appropriate clinical management of patients with a diagnosis of ASQUS.

We conclude that the Bethesda System provides an unambiguous, clinically useful classification for reporting squamous abnormalities. We believe that use of the term LSIL by itself is appropriate, whereas diagnoses of HSIL may be further specified as CIN2 or CIN3. The ASQUS designation should be reserved for morphologic abnormalities that are not clearly attributable to inflammation, but are not diagnostic of SIL. Management of patients with ASQUS will be optimized by providing descriptive comments when appropriate.

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## CORRECTION

### Incorrect Bibliographic Data in Two Articles

In the article entitled "Pathologists in the 1990s and in the 21st Century" that appeared in the June 1992 issue of the ARCHIVES (1992;116:563-566), an error appeared in reference 8, on page 566. The reference appeared as follows: "8. Linder J. Next-generation technologies: impact on the workload of the pathologist. *Arch Pathol Lab Med.* 1992. swk oa1027." The reference should have appeared as follows: "8. Linder J. Next-generation technologies: impact on the workload of the pathologist. *Arch Pathol Lab Med.* 1992; 116:586-589." Also in the June 1992 issue of the ARCHIVES, in the article entitled "Problems and Opportunities in Pathology Manpower" (1992;116: 593-598), an error appeared in reference 19, on page 598. The reference appeared as follows: "19. Vance RP, Hartmann WH, Prichard RW. Pathology trainee manpower: historical perspectives. *Arch Pathol Lab Med.* In press." The reference should have appeared as follows: "19. Vance RP, Hartmann WH, Prichard RW. Pathology trainee manpower: historical perspectives. *Arch Pathol Lab Med.* 1992;116; 574-577."